The main feature of Russell-Silver syndrome (RSS) is low birth weight followed by continued growth delays after birth. Individuals with RSS typically have proportionately short stature and normal head circumference. Certain characteristic facial features may also be present (triangular face, down-turned angles of the mouth, prominent forehead, prominent nasal bridge and a small jaw). Other variable features may be seen in children with RSS (see For More Information). Some individuals with RSS will have many of the possible characteristics associated with RSS while others will have very few.

RSS is a complex multigenic disorder caused by abnormalities in different genetic regions:

- In ~35% of RSS patients the cause is alterations in an imprinted growth regulatory gene, H19, on chromosome 11p15.5.
- Imprinting: Most autosomal genes are expressed (turned on) in both the paternally and maternally inherited gene copies. Imprinted genes are different in that they are expressed (turned on) in a parent of origin specific manner.
- H19 works to suppress or hold back growth. Usually, the maternal copy of H19 is expressed (on) and the paternal copy of H19 is methylated (off). Individuals with RSS due to H19 abnormalities have both the maternal AND paternal copies of H19 expressed (both on).
- In ~10% of RSS patients the cause is uniparental disomy (UPD) of chromosome 7. Patients with RSS due to UPD have two copies of chromosome 7 from their mother and no chromosome 7 from their father.
- In a small number of RSS patients other gene changes on chromosome 7 or the chromosome 11p15.5 region are found. Some of these are changes in gene copy numbers (duplications) or larger chromosomal rearrangements.

### Genetics

Methylation status: Methylation-specific Multiplex-Ligation-dependent Probe Amplification (MS-MLPA) is used to determine the methylation status of H19.

Gene Dosage Analysis: MLPA is used to determine the relative copy numbers of several genes in the 11p15.5 region.

Microsatellite analysis for UPD: A PCR-based microsatellite assay is used to compare the genetic material contributed from each parent on chromosome 7. Parental samples are required.

### Test Methods

**Who Should Be Tested?**

- Individuals suspected of having RSS.
- Fetuses at risk of having RSS (e.g. intrauterine growth retardation (IUGR), positive family history of RSS).

### Test Sensitivity

There are several molecular alterations associated with RSS. Testing with MLPA of 11p15.5 and UPD7 will detect about 49% of RSS patients. See the chart below for details.

### Etiologic Heterogeneity in RSS

<table>
<thead>
<tr>
<th>MLPA Testing of 11p15.5:</th>
<th>Copy number (11p15.5 region)</th>
<th>Methylation Status of H19</th>
<th>Methylation Status of KCNQ10T1</th>
<th>Freq.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypomethylation H19</td>
<td>Normal</td>
<td>Hypo</td>
<td>Normal</td>
<td>35%</td>
</tr>
<tr>
<td>Maternal duplication 11p15.5</td>
<td>Abnormal</td>
<td>Hypo*</td>
<td>Hyper*</td>
<td>~4%</td>
</tr>
</tbody>
</table>

**UPD Chromosome 7 Testing:**

<table>
<thead>
<tr>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal UPD 7**</td>
</tr>
</tbody>
</table>

*Depends on the extent of the duplication. **MLPA analysis of 11p15.5 will be normal if maternal UPD7 is detected.